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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/751,708

12/28/2000

David S. Terman

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02/15/2006

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EXAMINER

CANELLA, KAREN A

ART UNIT

PAPER NUMBER

1643

DATE MAILED: 02/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/751,708

Applicant(s)

TERMAN, DAVID S.

Examiner

Karen A. Canella

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-60 is/are pending in the application.
- 4a) Of the above claim(s) 1-23, 26-31 and 33-60 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 24, 25 and 32 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

DETAILED ACTION

1. Acknowledgement is made of applicant's election of Group IV, claims 24, 25 and 32 in the paper filed May 19, 2004. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). To clarify the record, and proceed with prosecution, the Species Election Requirement mailed January 7, 2004 is withdrawn.
2. Claims 1-60 are pending. Claims 1-23, 26-31 and 33-60, drawn to non-elected inventions, are withdrawn from consideration. Claims 24, 25 and 32 are under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
4. Claims 25 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
Claim 25 recites "receptors specific for lipid-based tumor associated antigens and superantigens". It is unclear if the properties of being specific for the lipid based tumor associated antigen and the superantigen are both to be attributed to the inhibitory receptor or if the properties are being referred to in the alternative rather than as a collective property. For purpose of examination both alternatives will be considered.
5. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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6. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Claim 32 is rejected with claim 24 to the extent that it depends on the rejected claim. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims is drawn to a method of treating cancer comprising the inactivating or deletion of immunocyte inhibitor receptors specific for lipid-based tumor associated antigens or superantigens. The claim reads on methods of gene therapy which require the targeting of a nucleic acid expressing antisense ITIMS to the appropriate effector cells in vivo, or targeting of a nucleic acid expressing an intrabody to the ITIM of the inhibitor receptor in vivo, as well as methods of ex vivo manipulation of immunocytes and the administration of the manipulated immunocytes to a patient with cancer. The specification is not enabling for the method as interpreted by any of the criterion above.

(A)As drawn to "immunocytes" and inhibitor receptors specific for lipid based tumor antigens and superantigens.

The specification provide no definition or “immunocytes”, therefore when given the broadest reasonable interpretation, the claims encompass the inhibition or deletion of the ITMS which are specific for lipid-based tumor associated antigens or superantigens in all immune cells such dendritic cells, B cells, monocytes, NK cells as well as T cells (for example, Cella et al, Journal of Experimental Medicine, 1997, Vol. 185, pp. 1743-1751). The specification does not identify a population of cells which has a inhibitor receptor which is specific for lipid-based tumor associated antigens or superantigens. The art teaches that the ITIMs are present on a wide variety of cells, and are specific for HLA molecules, rather than the antigen itself. The art teaches two T cell populations, one of which recognizes non-peptide, non-processed tumor antigens, which would fulfill the specific embodiment of “lipid-based tumor antigen”; the other of which is isolated from tumor draining lymph nodes and produces superantigen activated CTL, which would fulfill the specific embodiment of “specific for superantigens”. Because the art teaches that most of the inhibitory receptors recognize HLA rather than non-peptidic tumor antigens and superantigens (Falco et al, Journal of Experimental Medicine, 1999, Vol. 190, pp. 793-801), the scope of the enablement is not commensurate with the scope of the claim. One of skill in the art would be subject to undue experimentation in order to practice the broadly claimed method because one of skill in the art would be forced to find other inhibiting cell receptors which are specific for lipid-based tumor antigen or superantigens on any other type of immune cells before proceeding with the instant invention.

(B)As drawn to the administration of a nucleic acid in vivo

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art is that in vivo gene delivery is not well developed and is highly unpredictable. For instance, Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken

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up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and highly unpredictable in view of the complexity of in vivo systems. Orkin et al ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) state that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated. Until progress is made in these areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to the appropriate delivery and expression of an anti-sense construct in a patient. There is no

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guidance for how to provide the antisense construct to the appropriate cells and at the appropriate level to insure that the inhibitor receptor targeting will have a therapeutic effect. It is further noted that redundancy of the immunocyte inhibitory receptors is known (Blery et al PNAS, 1998, Vol. 95, pp. 2446-2451, especially page 1449, second column, lines 14-15 of the paragraph "Mutations of Tyr-794...."). Thus, it must first be proved in vitro that the inhibition will be reversed by the antisense construct for the inhibitory receptor. It is further noted that Mingari et al (Int J Clin Lab Res, 1997, Vol. 27, pp. 97-94) teach that the expression of non-inhibitory NKR could be harmful to the host in an anti-tumor response (page 91, lines 25-27 under "Conclusion"). Thus stressing the need that the deletion or inhibition of the inhibitor receptors be confined to a small subset of cells.

Further, the claim reads on the administration of a nucleic acid encoding an "intrabody" which would bind to the cytoplasmic portion of the ITIM of the inhibitor receptor. The art teaches that in order to produce intrabodies the nucleic acid sequences of minimally the complimentary determining region of said intrabody are necessary (Jones et al, Advanced Drug Delivery Reviews 1998, page 154, column 1, lines 18-26, and page 160, lines 24-25). The specification clearly fails to describe the nucleic acid sequences or the polypeptide sequences of intrabodies which would function to inhibit the activity of an immunocyte inhibitory receptor having ITIM regions, therefore one of skill in the art would be subject to undue experimentation in order to screen for antibodies which bind and inhibit the inhibitory receptor before being able to make the nucleic acid sequence encoding the intrabody regions. An intrabody by definition is an antibody that is expressed inside of a cell as a therapeutic agent (see abstract line 9). In order to get expression of an intrabody, especially in cells an efficient means of transferring the genes to the target cells is necessary (page 164, lines 1-3). Clearly, the specification fails to describe the necessary delivery vehicles for the insertion and expression of an intrabody in the desired immunocyte target for the reasons stated in section B above.

(C) As drawn to the administration of a cell transfected ex vivo

The instant claims read on an immunocyte having an inhibitor receptor specific for a tumor associated lipid antigen or a superantigen, in which said immunocyte were transfected with an antisense nucleic acid for said inhibitor receptor and the transfected cell administered to a patient having cancer.

It is known in the art that the presence of CTL in vivo or the generation of CTL in vivo does not have an absolute nexus with an anti-tumor response. The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, or failure of the host effector cells to reach the tumor due to the stomal barrier (Paul, *Fundamental Immunology*, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167).

Paul (*ibid*) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstract of Semino et al (*Journal of Biological Regulators and Homeostatic Agents*, 1993, Vol. 7, pp. 99-105 and the abstract of Algarra et al *International Journal of Clinical and Laboratory Research*, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. More currently, Bodey et al (*Anticancer Research*, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules. In the instant case, enablment reaches only to specific populations of T cells which are specific for tumor associated lipid and superantigens for the reasons set froth in section (A) above. Therefore loss of antigen presentation in the context of MHC will effectively render the tumor cell unrecognizable to the administered CTL lacking the inhibitor receptor.

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It is concluded based on the references discussed above, that the state of the art with respect to treating patients with cancer by means of administering immunocytes wherein the inhibitory receptors have been inactivated or deleted is unpredictable. The specification does not provide any disclosure that the administration of the claimed manipulated immunocytes would effectively treat a patient with a naturally occurring tumor. Thus, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed method of treatment.

7. Claims 24, 25 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to methods of inactivating or deletion of immunocyte inhibitor receptors specific for lipid-based tumor associated antigens or superantigens, comprising inactivation or deletion of nucleic acid encoding ITIMs of said specific receptors. The specification provides no definition of an "immunocyte", therefore when given the broadest reasonable interpretation, the claims encompass the inhibition or deletion of the ITMS which are specific for lipid-based tumor associated antigens or superantigens in all immune cells such dendritic cells, B cells, monocytes, NK cells as well as T cells (Cella et al, *ibid*). The specification does not describe a population of immunocytes having an inhibitor receptor which is specific for lipid-based tumor associated antigens and/or superantigens, nor does the specification describe the inhibitory receptor in terms of specific structural attributes of the extracellular domain which functions in the specific recognition of the lipid based tumor antigen or superantigen. The specification describes only the minimal cytoplasmic sequence motif, which is also recognized in the art as being common to any ITIM (for example, Yokoyama, *Journal of Experimental Medicine*, 1997, Vol. 186, pp. 1803-1808, see page 1803, second column, lines 7-9). The art teaches that the ITIMs are present on a wide variety of cells, and are specific for HLA molecules, rather than the antigen itself (Mingari et al, *ibid*, see pages 88-89 under the heading "The HLA class I specific NKR" and "Expression of HLA class I-specific

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inhibitory receptors in T lymphocyte subsets”). The art teaches two T cell populations, one of which recognizes non-peptide, non-processed tumor antigens, which would fulfill the specific embodiment of “lipid-based tumor antigen”(see art rejection below); the other of which is isolated from tumor draining lymph nodes and produces superantigen activated CTL, which would fulfill the specific embodiment of “specific for superantigens” (see art rejection below). Because of the breadth of the claims and the lack of a description in terms of the inhibitory receptor which would be required to practice the claims, the prior art disclosures of the two types of inhibitory receptors of T cells which separately interact with non-peptidic unprocessed antigens and superantigens fails to provide an adequate written description of the broad genus of inhibitory receptors which specifically bind to lipid based tumor associated antigens and/or superantigens as relied upon in the method claims. One of skill in the art would reasonable conclude that applicant was not in possession of the genus of inhibitory receptors with the required specificities. Because adequate written description has not been provided for the product on which the instant method claims rely, the method claims lack adequate written description.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 25 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Colonna et al (Journal of Experimental Medicine, 1997, Vol. 186, pp. 1809-1818) in view of Shu et al (Journal of Immunology, 1994, Vol. 152, pp. 1277-1288) and Hambor et al (PNAS, 1988, Vol. 85, pp. 4010-4014).

Claim 25 is drawn in part to a method of inactivation or deletion of receptors or ITIMs in immunocytes which inhibit cell activating receptors specific superantigens comprising

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inactivation or deletion of nucleic acids encoding ITIMs. Claim 32 embodies, in part, the method of claim 25 wherein the superantigen is a staphylococcal enterotoxin.

Colonna et al (Journal of Experimental Medicine, 1997, Vol. 186, pp. 1809-1818) teach the ILT2 inhibitory receptor on human lymphoid and myelomonocytic cells, activation of which inhibits superantigen-dependent T-cell mediated cytotoxicity (page 1813, second column, lines 6-19). Colonna et al does not teach the elimination or deletion of said receptor to generate or maintain superantigen-dependent T cell mediated cytotoxicity.

Shu et al teach a population of Vbeta T cells, isolated from a tumor draining lymph node of mouse transplanted with the MCA205 or 206 sarcoma cell line. Shu et al teach that said Vbeta T cells, which when stimulated by the SEB superantigen, generated therapeutic immune effector cells in vivo as evidenced by the decreased number of metastatic foci isolated from the mouse (Table III), but that the stimulated cells which comprised about equal numbers of CD+4 cells and CD+8 cells did not exhibit any cytotoxicity in a chromium-release assay in vitro (page 1283, under the heading "In vitro interactions of SEB-stimulated draining LN cells with specific tumor target cells").

Hambor et al teach the antisense inhibition of a CD+8 T cell receptor by means of an EBV based expression system.

It would have been prima facie obvious at the time the claimed invention was made to express an antisense mRNA for ILT2 in the Vbeta T cells isolated by the method of Shu et al. One of skill in the art would have been motivated to do so by the teachings of Colonna et al on the inhibitory effect of the ILT2 receptor on the cytotoxic activity of superantigen-stimulated T cells and the teachings of Shu et al that the superantigen stimulated T-cell population isolated from the tumor-draining lymph node did not demonstrate cytotoxicity in vitro. One of skill in the art would be motivated to understand the factor controlling the interaction between cytotoxic T cells and tumor cells. Elimination of the ILT2 receptors negative interaction by antisense methodology would provide an insight into the importance of this receptor in modulating the interaction between activated T cells and tumor cells.

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10. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Poccia et al (Journal of Immunology, 1997, Vol. 159, pp. 6009-6017) in view of Hambor et al (PNAS, 1988, Vol. 85, pp. 4010-4014).

Claim 25 is drawn in part to a method of inactivation or deletion of receptors or ITIMs in immunocytes which inhibit cell activating receptors specific for lipid-based tumor associated antigens comprising inactivation or deletion of nucleic acids encoding ITIMs.

Poccia et al teach that a subset of gamma delta T cells, mature V γ 9V δ 2, exhibit cytotoxicity against tumor cells and that the V γ 9V δ 2 receptor recognizes non-processed and non-peptidic phosphoantigens in a MHC-unrestricted manner (page 6009, second column, lines 10-14 and page 6011 second column, lines 13-16 under the heading "Involvement of the CD94/NKG2etpro for HLA class I..."). Poccia et teach that said subset of T cells are under the control of the NK-like CD94/NKG2 inhibitor receptor on addition to the TCR (page 6014, first column, lines 1-3). Poccia et al teach that about 40 effector cells to one target cell. Poccia et al do not teach the elimination or deletion of said CD94/NKG2 receptor.

Hambor et al teach the antisense inhibition of a CD+8 T cell receptor by means of an EBV based expression system tumor cell are required for at least %50 cytotoxicity (Figure 5).

It would have been prima facie obvious at the time the claimed invention was made to transfect the specific V γ 9V δ 2 T cells which recognize non-peptidic, non-processed tumor antigen with an antisense construct for the CD94/NKG2 receptor. One of skill in the art would have been motivated to do so by the teachings of Poccia et al on the presence of the inhibitory CD94/NKG2 on said cells. One of skill in the art would have been motivated to determine if deletion of the inhibitor receptor would result in a greater cytotoxic activity against the tumor cell target in the chromium release assay.

11. All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.


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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

2/6/2006


KARENA. CANELLA PH.D.
PRIMARY EXAMINER